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10/813,502	03/30/2004	Nicholas C. Nicolaides	MOR-0277	5311

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,502	NICOLAIDES ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70 and 72-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70 and 72-77* is/are rejected.

7)☒ Claim(s) *70 and 73* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/01/2007 has been entered.

2. Claims 1-69 and 71 have been cancelled. Claims 70, 73, 76, and 77 have been amended.

Claims 70 and 72-77 are pending and under examination.

3. The following nonstatutory obviousness-type double patenting rejections are withdrawn in response to submission of a terminal disclaimer by the Applicant on 10/01/2007:

The rejection of claims 70 and 72-77 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-7, and 12 of U.S. Patent No. 6,808,894, in view of Parkhurst et al.

The rejection of claims 70 and 72-77 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 6 of U.S. Patent No. 6,825,038, in view of Parkhurst et al.

The rejection of claims 70 and 72-77 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 8-10 of U.S. Patent No. 6,737,268, in view of Parkhurst et al.

The following rejections are withdrawn in response to Applicant's amendments to the claims filed on 10/01/2007:

The rejection of claims 70, 72, 73, 76, and 77 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The rejection of claims 70, 72, 73, 76, and 77 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The rejection of claims 70 and 72-77 under 35 U.S.C. 112, second paragraph, as being indefinite.

The rejection of claims 70, 73-75, and 77 under 35 U.S.C. 102(b) as being anticipated by Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641), as evidenced by Parkhurst et al.

The rejection of claims 70 and 73-77 under 35 U.S.C. 102(e) as being anticipated by Nicolaides et al. (U.S. Patent No. 6,146,894, of record), as evidenced by Parkhurst et al.

The rejection of claims 70 and 72-77 under 35 U.S.C. 103(a) as being unpatentable over Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641), in view of both Nicolaides et al. (U.S. Patent 6,825,038, of record) and Parkhurst et al.

The rejection of claims 70 and 73-77 under 35 U.S.C. 102(e) as being unpatentable over Nicolaides et al. (U.S. Patent No. 6,146,894), in view of both Nicolaides et al. (U.S. Patent 6,825,038) and Parkhurst et al.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 70 and 73-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-13 and 16-18 of U.S. Patent No. 6,146,894, in view of Parkhurst et al. (J Immunol, 1996, 157: 2539-2548, of record).

Although the conflicting claims are not identical, they are not patentably distinct from each other because are obvious variants.

The instant claims are drawn to **(i)** a method of making a genetically stable cell that produces a hypermutated immunogen by introducing into a first cell expressing a preselected immunogen *in vitro* the dominant negative allele PMS2-134, selecting the cells comprising a mutation in the preselected immunogen that results in enhanced antigenicity, and expressing the polynucleotide sequence encoding the preselected and mutated immunogen in a second, genetically stable cell, and **(ii)** a homogeneous culture of cells produced by this method (claims 70 and 77). The PMS2-134 gene is the human PMS2-134 (claim 73), the allele comprises a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 75), selecting is by determining that the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild type (claim 76).

The patent claims are drawn to: **(i)** a method of generating a mutation in a gene of interest (i.e., a preselected immunogen) by growing a population of mammalian cells expressing the gene of interest and a dominant negative allele of aPMS2 gene, wherein the dominant negative allele is a truncated human PMS2 (i.e., *in vitro* introduction, into the cell expressing a preselected immunogen, of a dominant negative allele of a PMS2 gene) and identifying a cell in which the preselected immunogen is mutated (i.e., selecting the cell), wherein the cell is hypermutable (i.e., a method of generating a hypermutated preselected immunogen) (claims 11 and 16-18). Identifying/selection is by analyzing the sequence of the gene of interest or of the mRNA transcribed from the

gene of interest (claims 12 and 13), i.e., determining whether the polynucleotide comprises a mutation as compared to the wild type, and **(ii)** a homogenous composition of cultured hypermutable, mammalian cells comprising a dominant negative allele of PMS2 (claim 7), wherein the dominant negative allele of PMS2 is human PMS2 (claim 8) comprising the first 133 amino acids of the human PMS2 (claims 9 and 10). The specification defines that the dominant negative allele of the human PMS2 is hPMS2-134 comprising codons 1-134 of the wild type hPMS2 (column 3, lines 27-32, Example 1), and therefore it is the same as the claimed truncated human PMS2 mutant, i.e., it has a truncation mutation at codon 134, wherein the truncation mutations is a thymidine at position 424 of the wild type hPMS2. It is noted that, since the claimed hPMS2-134 consists of codons 1-134 of the wild type hPMS2 it comprises the first 133 amino acids of the wild type hPMS2. With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method generates random mutations and that a number of mutations would result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the identifying/selecting step would necessarily render cells expressing a preselected immunogen with enhanced antigenicity. The patent claims do not recite expressing the mutated and enhanced immunogen into a second, genetically stable cell. However, this is not innovative over the prior art. Upon identification of the desired mutations in the pre-selected immunogen, one of skill in the art would have

been motivated to express the immunogen in a genetically stable cell in order to obtain continuous expression of the identified immunogen.

Thus, the patented claims 7-13 and 16-18 anticipate claims 70 and 73-77 of the instant application. Since the claims of the U. S. Patent No. 6,146,894 embrace all the limitations of the instant claims, the patent claims and the application claims are obvious variants of each another.

Applicant argues that the U. S. Patent No. 6,146,894 is not a proper reference for obviousness-type double patenting because the patent is not co-owned by Applicants and cite MPEP 804 to support this assertion.

In response to this argument, it is noted that Applicant is not the owner of the patent. Even if the patent and the instant application are not co-owned, the obviousness type double patenting rejection is proper because the instant application and the U. S. Patent No. 6,146,894 have a common inventor (see MPEP 804, Chart II-B).

New Rejections/Objections

Claim Objections

6. Claims 70 and 73 are objected to because of the following informalities: the claims recite PMS2-134, wherein PMS2-134 is the human PMS2-134. The recitation of PMS2-134 appears to be inconsistent with the definition in the specification wherein the human dominant negative PMS2 is defined as PMS134 and not as PMS2-134 (p. 26, lines 7-11); there is no literal support in the specification for the human PMS2-134 being

PMS2-134. However, the recitation of PMS2-134 in the claims does not introduce new matter because it is clear from the specification that the recitation of PMS134 is the same as the recitation of PMS2-134; PMS134 is PMS2-134, which is the dominant negative form of human PMS2

Appropriate amendment to the claims such that they are consistent with the definition in the specification is required.

7. Claim 73 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of claim 70. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 73 recites that the PMS2-134 is the human PMS2-134. However, as noted above PMS2-134 is the human PMS2-134, and therefore, claim 73 does not further limit the subject matter of claim 70.

Claim Rejections - 35 USC § 112, new matter

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 70 and 72-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, the amendment to the claim to recite a second, genetically stable cell, which expresses the mutated gene encoding the preselected hypermutated immunogen is considered new matter.

The specification does not provide support for a method of making a genetically stable cell by expressing a hypermutated preselected immunogen into a second cell which is genetically stable. The specification only provides support for a method of making a genetically stable cell by restoring the genetic stability of the first hypermutable cell by suppressing PMS2-134 expression (p. 5, lines 14-23).

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often

necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 70 and 72-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolaides et al. (Mol Cell Biol, 1998, 18: 1635-1641, of record), in view of each Nicolaides et al. (U.S. Patent 6,825,038, of record), Parkhurst et al. (J Immunol, 1996, 157: 2539-2548,of record), and Qin et al. (Oncogene, 1999, 18: 4394-4400).

The applied reference (i.e., U.S. Patent 6,825,038), has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and

that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Nicolaides et al. (Mol Cell Biol) teach a truncated human PMS2 mutant that has a truncation mutation at codon 134 (hPMS2-134), wherein hPMS2-134 has a dominant negative activity and confers a dominant negative MMR defect when transfected into cells (claims 70, 73, and 74) (p. 1635, column 1, p. 1640, column 1). It is noted that the hPMS-134 of Nicolaides et al. is the same as the one recited in the instant claims and therefore, it must comprise thymidine at nucleotide 424 as the truncation mutation (claim 75). Nicolaides et al. (Mol Cell Biol) also teach a method of producing a hypermutated β-galactosidase (i.e., hypermutated preselected immunogen) by introducing the hPMS2-134 into cells comprising a β-galactosidase reporter gene; introduction of hPMS2-134 into cells disturbs their MMR activity with a resulting higher frequency of mutations within the reporter gene, as opposed to the lack of mutations in the absence of PMS2-134 (claims 70 and 76) (p. 1636, column 2 bridging p. 1637, p. 1637, columns 1 and 2, p. 1638, column 1 and Table 1). Nicolaides et al. (Mol Cell Biol) teach cloning the cells comprising the gene encoding the mutated β-galactosidase, i.e., they teach selection for cells expressing the mutated β-galactosidase and a homogenous culture of these cells (claims 70 and 77) (p. 1637, column 2, p. 1638, column 1, Fig. 4). With respect to the limitation of selecting for cells comprising a

mutation resulting in enhanced antigenicity of the preselected immunogen (claim 70), it is noted that the method generates random mutations and that a number of mutations would necessarily result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the cloning step of Nicolaides et al. (Mol Cell Biol) would necessarily render cells expressing a preselected immunogen with enhanced antigenicity.

Nicolaides et al. (Mol Cell Biol) do not specifically teach expressing the hypermutated immunogen in a second, genetically stable cell, i.e., they do not teach a method of making a genetically stable cell that produces a hypermutated immunogen (claim 70). However, they do teach their method as being useful for molecular evolution (p. 1640, column 2, paragraph bridging p. 1641 and p. 1641, column 2). Nicolaides et al. ('038 patent) also teach a method for molecular evolution by using cells comprising PMS2-134 for molecular evolution (column 1, lines 54, 55, 64, and 65, column 2, lines 14-22, column 5, lines 65-67, and column 6, lines 1-7). In addition, the prior art teaches that introducing mutations into immunogens of interest results in immunogens with enhanced antigenicity (see Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Based on these teachings, it would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Nicolaides et al. (Mol Cell Biol) to obtain variants of immunogens of interest, select for variants with increased immunogenicity, and express them in a

genetically stable cell, with a reasonable expectation of success. One of skill in the art would have been motivated to express immunogens in a genetically stable cell in order to obtain continuous expression of immunogens with enhanced immunogenicity. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that protein antigens can be successfully expressed in cells with stable genome. Therefore, the combined teachings of Nicolaides et al. (Mol Cell Biol), Nicolaides et al. ('038 patent), and Parkhurst et al. disclose a method for making a genetically stable cell which produces a hypermutated immunogen.

Nicolaides et al. (Mol Cell Biol) taken with Nicolaides et al. ('038 patent) and Parkhurst et al. do not teach using a second DNA mutagen (claim 72). However, the prior art teaches that a combination between defective PMS2 activity and DNA mutagens results in a higher mutagenesis rate as compared to either defective PMS2 activity or DNA mutagens alone (see for example Qin et al., Abstract, p. 4399, column 2, last paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Nicolaides et al. (Mol Cell Biol) by additionally using DNA mutagens, with a reasonable expectation of success. The motivation to do so is provided by Qin et al., who teach a higher rate of mutagenesis in the presence of such agents. One of skill in the art would have been expected to have a reasonable expectation of success in using such because the art teaches the successful use of combinations between DNA mutagens and defective PMS2 to introduce mutations into DNA.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

12. Claims 70 and 72-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolaides et al. (U.S. Patent No. 6,146,894, of record), in view of both Parkhurst et al. and Qin et al.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Nicolaides et al. teach a method of generating mutations in a gene of interest (i.e., a preselected immunogen) by using hypermutable cells expressing the gene of

interest and the human PMS2-134, i.e., Nicolaides et al. teach a method for generating a hypermutated preselected immunogen; the method further comprises identification and selection of cells expressing the hypermutated preselected immunogen (claims 70, 73, and 76) (column 3, lines 50-67, column 4, lines 43-61, column 5 bridging column 6, column 6, lines 1-20, claims 1 and 3). Nicolaides et al. teach their human PMS2-134 as comprising a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 gene (claim 75) (column 4, lines 8-16, claims 5 and 6). With respect to the limitation of determining whether the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild type (claim 76), this is a requirement of the method, since in the absence of a comparison there would be no identification of any mutation. Nicolaides et al. also teach a homogenous composition of cultured hypermutable, mammalian cells obtained by the method above (claim 77) (column 5 bridging column 6, claim 7). With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method of Nicolaides et al. generates random mutations and that a number of mutations would result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the selecting step of Nicolaides et al. would necessarily render cells expressing a preselected immunogen with enhanced antigenicity.

Nicolaides et al. do not specifically teach expressing the hypermutated immunogen in a second, genetically stable cell, i.e., they do not teach a method of making a genetically stable cell that produces a hypermutated immunogen (claim 70). However, they do teach their method as being useful for molecular evolution (p. 1640, column 2, paragraph bridging p. 1641 and p. 1641, column 2). In addition, the prior art teaches the usefulness of introducing mutations into immunogens of interest to enhance their antigenicity (see Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Based on these teachings, it would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Nicolaides et al. to obtain variants of immunogens of interest, select for variants with increased immunogenicity, and express them in a genetically stable cell, with a reasonable expectation of success. One of skill in the art would have been motivated to express immunogens in a genetically stable cell in order to obtain continuous expression of immunogens with enhanced immunogenicity. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that protein antigens can be successfully expressed in cells with stable genome. Therefore, the combined teachings of Nicolaides et al. and Parkhurst et al. disclose a method for making a genetically stable cell which produces a hypermutated immunogen.

Nicolaides et al. taken with Parkhurst et al. do not teach using a second DNA mutagen (claim 72). However, the prior art teaches that a combination between DNA mutagens and defective PMS2 activity results in a higher mutagenesis rate as

compared to either DNA mutagens or defective PMS2 activity alone (see for example Qin et al., Abstract, p. 4399, column 2, last paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Nicolaides et al. by additionally using DNA mutagens, with a reasonable expectation of success. The motivation to do so is provided by Qin et al., who teach a higher rate of mutagenesis in the presence of such agents. One of skill in the art would have been expected to have a reasonable expectation of success in using such because the art teaches the successful use of combinations of DNA mutagens and defective PMS2 to introduce mutations into DNA. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

13. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

Art Unit 1633